Journal of Hematology & Thromboembolic Diseases

Arika et al., J Hematol Thrombo Dis 2016, 4:2
http://dx.doi.org/10.4172/2329-8790.1000236

Review Open Access

Hematological Markers of *In Vivo* Toxicity

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Rec date: February 29, 2016; **Acc date:** March 22, 2016; **Pub date:** 29 March, 2016

Abstract

In modern medical practice, toxicity studies are essential in assessment of safety of extracts or drugs used in clinical medicine. The interaction of the toxin or its metabolite with cellular constituents may bring about significant changes in hematological parameters. These alterations may be rapid or slow and often cause a change in structure and function of the affected tissues. In clinical laboratory setting these blood indices are assayed for the purpose of diagnosis, treatment or prevention of disease, and for greater understanding of the disease process. Therefore, assessment of hematological indices can be diagnostic of adverse effects of foreign compounds on the blood constituents since such hematological alterations have higher predictive value for human toxicity when the data are interpreted from animal studies.

Keywords Hematological markers; *In vivo* toxicity

Introduction

Systemic toxicity from therapeutic synthetic drugs and herbal medicines depends on the route of administration and site of exposure [1]. Cellular destruction causes direct tissue damage and this may have a biochemical, hematological or immunological basis. Many pathological lesions are of unknown mechanisms especially in the intermediate stages between the interaction of the toxin or its metabolite with cellular constituents and the start of the final degenerative changes that leads to cell death. Toxic effects may be detected using clinico-chemical analysis of body fluids or by gross pathological examination in the post mortem [2].

An increasing amount of attention is being directed towards the development and understanding of biological markers of *in vivo* toxicity. The biological markers enable the characterization of patient populations and quantitation of the extent to which therapies reach intended targets, alter proposed pathophysiological mechanisms and achieve clinical outcomes [3]. The potential to use biomarkers for identifying patients that are more likely to benefit or experience an adverse reaction in response to a given therapy, and thereby better match patients with therapies, is anticipated to have a major effect on both clinical practice and the development of new drugs and diagnostics [4]. Biomarkers can stratify patient populations or quantify drug benefit in primary prevention or disease-modification. Clinically, such biomarkers are required to inform regulatory and therapeutic decision making regarding the candidate therapies as they can directly contribute to detecting, quantifying and understanding the deleterious effect of exposure to a toxin [4].

The assessment of hematological parameters can be diagnostic of adverse effects of foreign compounds on the blood constituents of an animal [5]. Administration of the chemical compounds at toxic doses often results in changes in blood parameters that are indicative of hematological disorders such as anemia which is characterized by low hemoglobin content [6]; neutropenia which occurs in cases of reduced production of white blood cells or increased utilization and destruction, or both [7]; thrombocytopenia which precedes a reduction in the platelet count as a result of decrease in platelet production, decline in platelet survival, and dilution of platelet numbers resulting from transfusion of platelet-poor blood; and malignancies such as leukemia, lymphoma and myeloma [8,9].

Blood, a carrier of metabolic products from and to the various regions of the cardiovascular system, is affected by the clinical status of the tissue environment [10]. Due to the addition of altered biochemical and tissue products in the blood and their interactions with the blood constituents, the functional properties of hematological parameters are changed [11]. Blood parameters are key indicators in diagnosing the actual physiological status of an organism [12]. An organism must keep its blood composition and constituents relatively constant under natural conditions to function properly [12]. This article reviews the hematological parameters that are diagnostic of blood disorders and their alterations due to deleterious effect of the toxin since hematological changes have higher predictive value for human toxicity [13].

Erythrocytes and Related Parameters

Red blood corpuscles (RBCs)

Red blood corpuscles (erythrocytes) are enucleate cells that are packed with the oxygen-carrying protein, hemoglobin. Under normal conditions, the concentration of erythrocytes in blood is approximately 3.85-5.16 million/μL in women and 4.54-5.78 million/μL in men [14]. A decrease in number of red cells in the blood is often associated with development of anemia [14]. This could be due to the stimulation of lipid peroxidative system by the toxin resulting in production of lipid peroxides which hemolyses the RBC's especially in diabetic patients [15]. The major pathological consequences of free radical induced membrane lipid peroxidation include increased membrane rigidity, attenuation/inhibition of anti-inflammatory cytokine production like the adiponectin, increased cellular deformation, reduced erythrocyte survival via increased self-necrosis, and increased lipid fluidity which

starts a chain of inflammatory reactions causing endothelial dysfunction [15].

A primary increase in bone marrow activity causes polycythemia (erythrocytosis). This occurs due to the myeloproliferative disorder or in response to increased erythropoietin production either as a consequence of chronic hypoxemia or because of inappropriate erythropoietin secretion, especially the lung or renal disorders [16]. Elevated level of erythrocyte indices can be used as potential indicators in finding the risk of developing micro and macro vascular complications especially in diabetic patients [17]. Other common causes of high RBC values include smoking, exposure to carbon monoxide, chronic kidney disease, liver disease, certain forms of heart disease, lung disease and alcoholism. Conditions that influence water content of the body such as diarrhea or vomiting, excessive sweating, dehydration, use of diuretics and the severe burns may also cause elevated RBC values [18].

Hemoglobin (Hb)

Hemoglobin is the primary intracellular protein of the RBCs; binds oxygen in the pulmonary artery for transport to tissues and binds tissue carbon dioxide for transport back to lungs for exhalation [19]. It is synthesized in the bone marrow. Hemoglobin is a conjugated protein containing heme as prosthetic group and globin as the protein part apoprotein [20]. The normal concentration of Hb in an adult varies from 12.0 to 17.2 g/dL. Approximately 90 mg/kg of Hb is destroyed in the body every day. Hb has a molecular weight of about 67, 000. Each gram of Hb contains 3.4 mg of iron [20]. Heme is produced by the combination of iron with a porphyrin ring and is present as a prosthetic group in hemoglobin as well as myoglobin, cytochromes, peroxidases, catalases and tryptophan pyrrolases [20].

Low levels of hemoglobin arise as a result of loss of blood (hemorrhage) or immature reticulocytes usually related to iron deficiency in the diet; or accelerated blood cell destruction, leading to anemia [14]. Alterations in hemoglobin molecules also results in sickle cell disease. Sickle cell disease is characterized by viscous sickle-shaped erythrocytes that become rigid with a shortened life span often leading to profound anemia [14]. The increased levels of free hemoglobin in blood (hemoglobinemia) might be as a result of massive hemolysis of the red blood cells following inflammation or an antibody attack on the red blood cells especially when there is a high differential leucocyte counts in blood [21].

Hematocrit (PCV)

Hematocrit represents the percentage of red blood cell volume of whole blood volume (called Packed Cell Volume (PCV) in animals and is clinically used to signal known or suspected anemia [19]. Factors influencing RBCs will affect the hematocrit because RBCs comprise 99% of the total cells of the blood [19]. Reference values are 42-52% for males and 36-48% for females. The hematocrit is usually about 3 times the hemoglobin value (assuming there is no marked hypochromia). An abnormally high hematocrit is representative of polycythemia. The increased levels of hematocrit may be as a result of hyperosmotic conditions due to high dosage levels of toxin, elevated levels of WBCs, hypoxia, chronic alcoholism, vitamin B12 deficiency and folate deficiency. The average error in hematocrit is about 1-2%. The hematocrit may be changed by altitude, position, and heavy smoking, in the same manner as the hemoglobin may be changed.

Hematocrit is positively correlated with hyperinsulinemia and risk factors associated with insulin resistance, such as high blood pressure, elevated serum triglycerides, low HDL cholesterol, and central obesity and could therefore be related to insulin resistance. Hematocrit is a major determinant of blood viscosity. Increased blood viscosity also contributes to the development of insulin resistance [22-26]. A lower than normal hematocrit is representative of anemia especially the Aplastic anemia and some thalassemia syndromes. This can result from a decrease in the number of erythrocytes, a decrease in the amount of hemoglobin in each erythrocyte, or both. It is usually acquired as a result of damage to the myeloid tissue by chemicals, (such as, benzene), other toxins, medications (certain antibiotics and sedatives), or gamma radiation; all of which inhibit enzymes needed for hemopoiesis. The three hallmarks of aplastic anemia are erythropenia (especially low crit), markedly decreased hemoglobin, and leukopenia (with ALL WBC values markedly "off") [27].

Mean cell/corpuscular volume (MCV)

MCV is a measure of the average volume or size of a red blood cell. The reference range for MCV is 78.5-96.4 fL/red cell in adult although the reference ranges may vary depending on the individual laboratory and patient's age [20](Table 1). MCV is elevated or decreased in accordance with average red cell size; low MCV indicates microcytic (small average RBC size), normal MCV indicates normocytic (normal average RBC size), and high MCV indicates macrocytic (large average RBC size). Low MCV is consistent with iron deficiency, microcytic anemia and thalassaemia syndromes while values above the reference range are found in chronic alcoholism, vitamin B12 deficiency and folate deficiency [28].

Mean cell haemoglobin (MCH)

Mean corpuscular hemoglobin (MCH) is a calculation of the average amount of hemoglobin inside a single red blood cell [20]. The reference range is 27-33 pg (pictograms). Values below this range are found in iron deficiency, thalassaemias and in some cases of anemia in chronic diseases. MCH is increased in macrocytic anemias [29].

Mean corpuscular hemoglobin concentration (MCHC)

Mean corpuscular hemoglobin concentration (MCHC) is a calculation of the average concentration of hemoglobin inside a single red blood cell. The reference range is 32.6-37.7 g/dL [20]. It is mainly used in the diagnosis of iron deficiency. A low MCHC is a sensitive indicator of iron deficiency only when it is calculated using a PCV determined by hematocrit method, or when it is obtained from a Technicon H1 series automated cell counter. It is not a sensitive indicator of iron deficiency when obtained from a Coulter counter since under this circumstances MCHC values only fall consistently below normal when the Hb is below 7 g/dL. The decreased levels MCHC values might also be an indication of abnormal hemoglobin synthesis, failure of blood osmoregulation and plasma osmolarity [30]. When MCHC level are increased it is an indicator of hereditary spherocytosis [31].

The above hematological indices especially the RBC, PCV, and Hb are associated with the total population of the red cells; MCV reflects the size of red blood cells while MCH and MCHC are used mathematically to define the concentration of hemoglobin and to suggest the restoration of oxygen carrying capacity of the blood [32].

Therefore, reduced levels of MHC and MCHC reflects diminished oxygenation of tissues resulting in tissue hypoxia.

Anemia is a pathologic condition characterized by blood concentrations of hemoglobin below normal values. Anemia may be caused by loss of blood (hemorrhage); insufficient production of red cells with insufficient hemoglobin related to iron deficiency in the diet; or accelerated blood cell destruction [33].

Hematology Reference Ranges (Peripheral Blood)		
Blood Indices	Adult Male	Adult Female
WBC (10^9/L)	3.7-9.7	3.9-11.7
RBC (10^{12}/L)	4.54-5.78	3.85-5.16
HGB (g/dL)	13.3-17.2	12.0-15.0
HCT %	38.9-50.9	34.8-45.0
MCV (fL)	81.2-94.0	78.5-96.4
MCHC (g/dL)	32.6-37.7	32.2-35.9
RDW %	11.5-14.1	11.3-14.7
HDW (g/dL)	2.38-3.15	2.00-2.98
PLT (10^9/L)	179-373	172-440
MPV (fL)	6.1-8.9	6.3-9.1
Neu %	42.9-78.4	39.6-74.7
LYMPH %	14.1-45.8	21.1-52.8
Mono %	3.3-9.2	2.7-6.6
Eosin %	0.3-6.2	0.5-7.2
Baso %	0.3-1.3	0.2-1.0
NEU 10^9/L	2.0-6.7	1.9-7.9
LYMPH 10^9/L	1.1-3.3	1.3-3.6
MONO 10^9/L	0.2-0.7	0.2-0.5
EOS 10^9/L	0.0-0.4	0.0-0.4
BASO 10^9/L	0.0-0.1	0.0-0.1
Retic %	1.1-2.7	0.9-2.4
Retic ABS 10^9/L	55.1-140.7	40.6-111.8
CHr (pg)	29.0-35.3	27.5-34.2

Table 1: Hematology reference ranges.

Anemia can be classified from three points of view: pathogenesis, red cell morphology, and clinical presentation. Pathogenic mechanisms involve inadequate production and loss of erythrocytes as a result of bleeding or hemolysis. Based on these, anemia can be divided into two types. Hypo-regenerative when bone marrow production is decreased as a result of impaired function, decreased number of precursor cells, reduced bone marrow infiltration, or lack of nutrients. The other is regenerative when bone marrow responds appropriately to a low erythrocyte mass by increasing production of erythrocytes. In practice, classification based on basic parameters of red cell morphology such as mean corpuscular volume (MCV), allows for a quicker diagnostic approach [34].

Anemia can also be classified according to the form of clinical presentation as acute (bleeding or hemolysis) or chronic. Anemia can be classified as microcytic, normocytic or macrocytic depending on MCV [34]. MCV has a relationship with mean corpuscular hemoglobin (MCH), which reports on the mean hemoglobin per erythrocyte expressed in pictograms. Therefore, MCV and MCH decrease is stated as microcytic, hypochromic anemia while an increase is macrocytic, hyperchromic anemia. The MCH concentration (MCHC) reports on the average concentration of hemoglobin in each erythrocyte expressed as a percentage and its variations are very small, even in the presence of hypochromia [35].

Leucocytes and Related Parameters

White blood cells (WBC)

White blood cells count and its indices play a vital role in immune function. They are formed from pluripotent hematopoietic stem cells found in the red bone marrow (myeloid). Myeloid stem cells give rise to platelets, and all WBC's except lymphocytes. Lymphoid stem cells give rise to lymphocytes. Some of the hematopoietic growth factors that stimulate hematopoiesis include, thrombopoietin which increases the number of platelet precursors and cytokines (colony stimulating factors and interleukins) which increases the number of WBC precursors. Two unique features of the immune system are the ability to generate antigenic specificity and the phenomenon of immunological memory [36]

White blood cells (leukocytes) provide immunity to the body against antigen invasion. They are classified on the basis of the type of granule in their cytoplasm and the shape of the nucleus. Therefore, white blood cells are classified into two groups including: granulocytes (polymorphonuclear leukocytes) and agranulocytes (mononuclear leukocytes). Neutrophils, eosinophils, and basophils are examples of granulocytes (terminal cells) while agranulocytes include the lymphocytes and monocytes which can also undergo through several cycles of activity before dying [33]

Peripheral blood leukocytes are composed of polymorphonuclear cells, including monocytes, neutrophils, basophils, eosinophils as well as lymphocytes. Polymorpho- and mononuclear leukocytes can be activated by advanced glycation end-[37], oxidative stress [38], angiotensin II [39], and cytokines [40] in a state of hyperglycemia.

The lymphocytes help to specifically recognize a diverse range of antigens, differentiate and mature to functional capacity, respond to the antigens and establish immunologic memory [41]. Neutrophils and monocytes have phagocytic activities [42]. They attack and destroy foreign particles, cell waste materials and bacteria. Eosinophils detoxify foreign proteins that emanate from the lungs and intestinal tract, especially in the later stages of inflammation. Basophils contain heparin, histimine, and serotonin, and are thought to stimulate blood flow to injured tissues, simultaneously preventing excessive bleeding [43].

Neutrophils (NEU)

Neutrophils are polymorphonuclear leukocytes constituting 60-70% of circulating leukocytes in humans. They are short-lived cells with a half-life of 6-7 hours in blood and a life span of 1-4 days in connective

tissues. After which they then die, whether or not they have engaged in phagocytosis activity; hence termed as terminal cells. Neutrophiles contains myloperoxidase, acid phosphatase and other acid hydrolases at primary stage of development while the secondary granules contains collagenase, lactoferrin and lysosomes. The neutrophils defend the body against invasion by microorganisms, especially the bacteria [33].

Neutrophils kill microorganisms through two mechanisms; by oxygen dependent mechanism which involves the production of hydrogen peroxide and the superoxide anion by the enzyme NADH oxidase and oxygen independent mechanisms that eliminates the pathogens through intracellular acid pH, or enzymes lysozyme and lactoferrin that are contents of the secondary granules [33].

Clinically, an increase in neutrophils in the blood (i.e neutrophil 'leucocytosis' or 'neutrophilia') is usually as a result of an infection and tissue injury. The mechanism responsible for leukocytosis is the stimulation of activities of leptin and the leptin receptor that are parts of a pathway that stimulates hemopoiesis [44]. The other pathological causes of neutrophilia include, Bacterial infections; Inflammation or necrosis; Metabolic disorders e.g. diabetic ketoacidosis, uremia, and eclampsia; Steroid therapy; Acute hemorrhage or hemolysis.

Reduced levels of neutrophils in the blood (neutropenia) are seen in a wide range of inherited and acquired disorders [43] such as Kostmann's syndrome, Myelokathexis and Leukemia. Neutropenia can also be caused by infections such as Hepatitis A, B and C, malaria, HIV/AIDS and vitamin deficiencies; antibody attack on neutrophil-specific antigens (NA, NB) and direct toxicity or immune-mediated damage by drugs such as anti-inflammatory, antibacterial, anticonvulsant, antithyroid, antihypertensive drugs and oral hypoglycemic agents.

Monocytes (MON)

Monocytes are agranulocytes found in the blood representing the recently formed precursors of the mononuclear phagocyte system. Monocytes differentiate into macrophages after they enter connective tissues and interact with lymphocytes and play an essential role in the recognition and interaction of immunocompetent cells and antigen [33]. The half-life of the monocyte in the blood is 12-100 hours. Chronic bacterial infections such as tuberculosis, inflammation and malignant disorders result in monocytosis while corticosteroid treatment is often associated with monocytopenia [43].

Monocytes (MON) are crucial cells in the genesis of atherosclerotic lesions, as they stick to endothelium, which results in cardiovascular disease. Possible mechanism of increase in oxidative stress in PMNs and MON in relation to diabetes, hypertension and CRP remains to be elucidated. High blood Pressure and high glucose are reported to trigger protein kinase C activation, which may play a role in increasing PMN oxidative stress induced by hypertension and diabetes [45].

Lymphocytes (LYM)

Lymphocytes are the immunologically competent cells that assist the phagocytes in defense of the body against infection and other foreign invasion. The bone marrow and thymus are the primary lymphoid organs in which lymphocytes develop. The secondary lymphoid organs in which the specific immune responses are generated are the lymph nodes, spleen and lymphoid tissues of alimentary and respiratory tracts [36].

Lymphocytes constitute B and T lymphocytes. T lymphocytes make up 75% of the lymphocytes of the blood and participate in cell-mediated immunity whilst B lymphocytes releases antibody against a specific antigen (humoral immunity). T lymphocytes are less autonomous than B lymphocytes and interact with antigen presenting cells expressing self-histocompatibility molecules human leucocyte antigens (HLA) for the recognition of the antigen by the T cell receptor (TCR) [43].

B lymphocytes are responsible for humoral immunity and following an appropriate antigenic stimulus, they transform into plasma cells and secrete antibody specific to that antigen [43]. Within the lymphoid tissues, such as lymph nodes and spleen, B cells undergo a morphological transformation into immunoblasts and, ultimately, plasma cells upon stimulation by an antigen [43].

T lymphocytes originate in the marrow but many are destroyed in subsequent processing by the thymus, the objective being to select the minority of the cells which recognize self-HLA but not react with self-tissue antigens. Mature T cells are divisible into three basic types. Around two thirds of the bloods T cells are "helper" cells expressing the surface marker CD4, whilst the remainder express CD8 and are mostly 'cytotoxic' type [43]. B lymphocytes are responsible for humoral immunity. Following an appropriate antigenic stimulus, they transform into plasma cells and secrete antibody specific to that antigen. B cells are derived from the stem cells of the bone marrow. Each cell can be defined by its expression of membrane and cytoplasmic antigens in addition to the stage of immunoglobulin gene rearrangement. Within the lymphoid tissues, such as lymph nodes and spleen, B cells can be stimulated by antigen to undergo a morphological transformation into immunoblasts and, ultimately, plasma cells [43].

Lymphocytosis occurs when absolute lymphocyte count is >4000/cmm. Levels are higher in infancy and gradually decrease toward adult levels. Causes of lymphocytosis include, acute infections: pertussis, hepatitis, infectious mononucleosis; chronic infections: tuberculosis, congenital syphilis and lymphoma or leukemia.

Eosinophils (EOS)

Eosinophils are granulocytes that develop during hematopoiesis in the bone marrow before migrating into blood. Eosinophils play two roles in your immune system: Destroying foreign substances and regulating inflammation. A high number of eosinophils (eosinophilia) defined as an absolute eosinophil count $>0.7\times10^9$/l are often linked to a variety of disorders [19]. A high eosinophil count may be due to: Allergic disease; parasite infection, such as worms; certain fungus infections; Asthma; Autoimmune diseases; Eczema; Hay fever; Leukemia and other blood disorders such as Chronic myeloid leukemia; Pernicious anemia and Hodgkin disease. A lower-than-normal eosinophil count may be due to: Alcohol intoxication; Overproduction of certain steroids in the body (such as cortisol) [19].

Basophils

Basophils have many dark cytoplasmic granules which overlie the nucleus and contain heparin and histamine. In the tissues they become mast cells. They have immunoglobulin E (IgE) attachments sites and their degranulation is associated with histamine release. Therefore, they are involved in IgE mediated hypersensitivity reactions. Subsequent to reaction between allergen and IgE the release of basophil granule contents such as histamine, lead to the recognized clinical features of allergy or hypersensitivity. An increase in blood

basophils above 0.8×10^9 indicates myeloproliferative disorder such as chronic myeloid leukemia or polycythemia vera. Reactive basophil increases are sometimes seen in myxedema, during smallpox or chickenpox infection and in ulcerative colitis [36].

Platelets

Thrombopoietin stimulates myeloid stem cells to produce platelets. Myeloid stem cells develop into megakaryocyte-colony-forming cells that develop into megakaryoblasts. Megakaryoblasts transform into megakaryocytes, which ultimately fragment. Each fragment, enclosed by a piece of cell membrane, is a platelet (thrombocyte). Normal blood contains 250,000 to 400,000 platelets/μL. Platelets have a life span of only 5 to 9 days. Aged and dead platelets are removed by fixed macrophages in the spleen and liver. Platelets are responsible for coagulation [46]. When bleeding occurs, the platelets swell, clump together, and form a sticky plug that helps stop the bleeding. If there are too few platelets, uncontrolled bleeding may be a problem. If there are too many platelets, there is a chance of a blood clot forming in a blood vessel. Platelets may be involved in hardening of the arteries especially during atherosclerosis.

The rise in platelets count seen may suggest that the extracts have a stimulatory effect on thrombopoietin [47]. They, therefore, can be used in management of hemophilia. The cause of increased platelet count (thrombocytosis) in mice models may be associated with inflammation and presence of a blood disease such as abnormal bleeding induced by toxic phytochemical substances such as tannins in the administered drugs or alternative medicines. Circulating platelets can be reduced (thrombocytopenia) by one or more of the following processes: trapping of platelets in the spleen, decreased platelet production or increased destruction of platelets.

Platelet hyperactivity results in increase in Mean platelet volume (MPV) due to increased number of platelet glycoprotein receptors on the platelet membrane, the thromboxane synthesizing capability and the platelet granule secretions [48]. Platelets are produced in bone marrow and thus can be decreased in bone marrow disease and after excessive chemotherapy or anemias caused by B12 deficiency. Decreased values can result in spontaneous bleeding. Low platelets values can occur in pregnancy or idiopathic thrombocytopenic purpura (ITP) and other situations that destroy platelets. Large spleen can lower the platelet count [49].

Several clinical studies have shown that high blood sugar levels in diabetic patients indicate an altered (increased) population of circulating platelets compared with non-diabetics. This is because of the fact that, in addition to thrombopoietin (a chief hormonal regulator of platelet production) nitric oxide which is generated during oxidative stress in diabetes, can also stimulate platelet production [50]. Distorted platelet morphology and function have also been reported in patients with Diabetes Mellitus [51].

An early finding showed that diabetic platelets exhibit enhanced arachidonic acid- thromboxane production. Thromboxane (TXA2), an effective platelet activating and vasoconstriction agent, is produced from the arachidonic acid and has a positive correlation with glucose level. Therefore, elevated glucose level in diabetes may encourage the platelet activation [52]. Upon activation, platelets change from a discoid to a sphere-shaped with long, spiky pseudopods. Consequently, the platelets are larger and more activated, expressing higher levels of the adhesion receptors like GPIIb/IIIa. Activated platelets show an increased adhesiveness and aggregation, and are a threat factor for developing coronary thrombosis, leading to myocardial infarction [48]. Moreover, efficient platelet abnormalities in DM have been linked with various 'intracellular' platelet alterations, hence diabetic platelets have increased Ca^{2+} ATPase activity resulting in high intracellular Ca^{2+} concentrations and platelet hyperactivity [53]. Therefore, it can be concluded that variation in platelet morphology and functions are linked with pathological processes and greater risk of vascular complications in patients with diabetes [52]. Elevated HbA1c level in diabetics shows that the higher the blood glucose concentration the greater will be chance of glucose molecules that bound to hemoglobin which may affects the proper functioning of hemoglobin and concern with diabetic complications [54].

Mean platelet volume (MPV)

Mean platelet volume measures the average amount (volume) of platelets. Mean platelet volume is used along with platelet count to diagnose some diseases. If the platelet count is normal, the mean platelet volume can still be too high or too low. MPV is an indicator for an increased platelet activity and thus thrombogenic activation, which may play a role in the development of vascular complications in persons with type 2 diabetes. A recent study found that MPV was significantly higher in persons with diabetes than in non-diabetic persons and that MPV was strongly correlated to fasting and postprandial glucose levels as well as HbA1c values [48].

Conclusion

The bioavailability of the chemical compounds at toxic levels in biological media induces alteration in various hematological indices. Hematological constituents have been elucidated as pathological reflectors of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention and hence change in relation to the physiological status of an individual. For instance, administration of diclofenac at toxic levels to adult male rats induced significant reduction on Hb, PCV, RBCs and WBCs values within 2-4 weeks [55]. Valproic acid has been shown to have some haematological toxicity. Valporic acid is able to alter hematopoiesis by inhibition of erythroid differentiation in the experimental K562 cell linkage [56].

Lead poisoning is a known cause of microcytic anemia [57]. Katavolos et al. also demonstrated that MCHC and hemoglobin concentration in two avian species decreased significantly with rising blood lead concentration [58]. Almost all classes of psychotropic agents such as clozapine olanzapine and other atypicals have been reported to cause blood dyscrasias. Their mechanisms of action include direct toxic effects upon the bone marrow, the formation of antibodies against haematopoietic precursors or involve peripheral destruction of cells [59].

Excessive alcohol consumption also causes hypocellularity leading to anaemia, leucopenia, thrombocytopenia and their relative sequelae [60]. Chronic alcoholism has been linked to insufficient availability of iron and other vital micronutrients such as vitamin B12 and folate for erythropoietic activities [61]. This is probably due to the inability of the ethanol irritated sticky intestinal mucosa to absorb these essential blood forming micronutrients, which eventually result in impaired haemopoiesis [61]. Therefore, clinical laboratory measurement of blood indices is key in assessment of deleterious effect of the toxin since hematological changes have higher predictive value for human toxicity.

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